Acute Lower Respiratory Infections Associated With Respiratory Syncytial Virus in Children With Underlying Congenital Heart Disease: Systematic Review and Meta-analysis

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SUPPLEMENT ARTICLE

Acute Lower Respiratory Infections Associated With Respiratory Syncytial Virus in Children With Underlying Congenital Heart Disease: Systematic Review and Meta-analysis

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Background. Respiratory syncytial virus (RSV) is the most common viral pathogen associated with acute lower respiratory infections (ALRIs), with significant childhood morbidity and mortality worldwide. Estimates reporting RSV-associated ALRI (RSV-ALRI) severity in children with congenital heart disease (CHD) are lacking, thus warranting the need to summarize the available data. We identified relevant studies to summarize the findings and conducted a meta-analysis of available data on RSV-associated ALRI hospitalizations in children aged <5 years, comparing those with underlying CHD to those without CHD.

Methods. We conducted a systematic search of existing relevant literature and identified studies reporting hospitalization of children aged <5 years with RSV-ALRI with underlying or no CHD. We summarized the data and conducted (where possible) a random-effects meta-analysis to compare the 2 groups.

Results. We included 18 studies that met our strict eligibility criteria. The risk of severe RSV-ALRI (odds ratio, 2.2; 95% confidence interval [CI], 1.6–2.8), the rate of hospitalization (incidence rate ratio, 2.8; 95% CI, 1.9–4.1), and the case-fatality ratio (risk ratio [RR], 16.5; 95% CI, 13.7–19.8) associated with RSV-ALRI was higher among children with underlying CHD as compared to those without no CHD. The risk of admission to the intensive care unit (RR, 3.9; 95% CI, 3.4–4.5), need for supplemental oxygen therapy (RR, 3.4; 95% CI, .5–21.1), and need for mechanical ventilation (RR, 4.1; 95% CI, 2.1–8.0) was also higher among children with underlying CHD.

Conclusion. This is the most detailed review to show more-severe RSV-ALRI among children aged <5 years with underlying CHD, especially hemodynamically significant underlying CHD, as compared those without CHD, supporting a need for improved RSV prophylactics and treatments that also have efficacy in children older than 1 year.

Keywords. Respiratory syncytial virus; acute lower respiratory infections; congenital heart disease.

Respiratory syncytial virus (RSV) is the most common viral pathogen identified in children with acute lower respiratory infections (ALRIs), with significant childhood morbidity and mortality worldwide [1–3]. It is estimated that RSV was associated with a global burden of 33.1 million cases of ALRI and 3.4 million admissions in 2015 [4]. There is no specific treatment or vaccine available for RSV infection at the moment, but immunoprophylaxis with palivizumab has been available for prevention of RSV infection in high-risk groups since 1998 [5, 6]. The high-risk groups include children born prematurely, those with bronchopulmonary dysplasia, congenital heart disease (CHD), and some immunodeficiency conditions, with higher rates of hospitalization, morbidity, and mortality in all groups [7, 8].

Several studies have demonstrated the severity of RSV disease in children with underlying CHD. For example, a higher risk of RSV hospitalization (incidence rate ratio [IRR], 1.7; 95% confidence interval [CI], 1.5–2.0 [9]) and a higher risk of intensive care unit (ICU) admission (odds ratio [OR], 3.1; 95% CI, 1.1–8.3 [10]) among children with underlying CHD as compared to those without CHD. Palivizumab has been demonstrated to reduce RSV hospitalizations among children with hemodynamically significant underlying CHD by 45% and the length of hospital stay (LOS) by up to 76% [11]. There remains, however, variation between and within countries regarding the recommendation for the use of palivizumab as prophylaxis for infants with underlying CHD [12–14].

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A recent review summarized data on morbidity and mortality of RSV infection among children with CHD [15], but it did not include some important studies [1, 7, 16–18] or conduct a meta-analysis for the reported outcomes. In our analysis, we reviewed the available data and conducted a meta-analysis to provide estimates of RSV-ALRI severity among children with underlying or no CHD. This will likely generate simpler conclusions that are useful for comparative purposes and decision making.

METHODS

Search Strategy

We systematically searched for existing relevant literature in the MEDLINE, EMBASE, and Global Health databases, using well-defined search terms (Supplementary Table 1), without restrictions on country or time of publication. The search was completed on 3 April 2017. Two authors (P. S. C. and S. W. L. W.) conducted the literature search and data extraction independently. Any disagreements were arbitrated by H. N. The study was registered with PROSPERO (registration number CRD42017060361; available at: https://www.crd.york.ac.uk/prospero/).

Definition and Selection Criteria

We searched for information on hospitalization data (ie, rates and age at admission) among children aged <5 years with RSV-ALRI with and without underlying CHD. We also searched for information on mortality rate, LOS, need for supplemental oxygen therapy, mechanical ventilation, ICU admission, and risk of severe RSV-ALRI (which included clinical signs of severe disease, such as apnea, abnormal blood gas levels, LOS >5 days, need for supplemental oxygen therapy or mechanical ventilation, as defined by the included publications for the multivariable analysis) among both groups of children. Studies were initially screened by using their titles and abstracts. The full texts of the selected studies were then reviewed for eligibility.

Publications were eligible for inclusion if they reported data on children who were hospitalized with RSV-ALRI, were aged <5 years, and reported data on children with both underlying as well as CHD (those reporting data only for children without CHD were excluded) and if they provided the full text of the article in English. Publications were excluded if they involved children aged >5 years or did not specify participants' age; were conference abstracts, reviews, or case notes; reported data on prophylaxis for, prevention of, and treatment of RSV infection without providing specific data for the outcomes of interest for underlying CHD; reported data on RSV-ALRI as a coinfection, rather than a primary outcome; reported data on CHD as a comorbidity or part of a syndrome, rather than a specific underlying disease; and/or provided data on cases of bronchiolitis (without laboratory confirmation of RSV-ALRI).

Data Extraction and Analysis

We extracted data by using a standardized data-extraction template. For placebo-controlled studies, we used the placebo arm to extract data. We extracted the means, medians, and percentages and measurements of risk. We adopted the GRADE method of scoring [19] to assess the quality of the included studies (Supplementary Tables 2 and 3) and obtained the overall score as an average of the scores from the individual studies.

We conducted a meta-analysis of the data by using Stata, version 12 (Stata, College Station, TX). We reported risk ratios (RRs) for hospitalization and ICU admission rates, the need for supplementary oxygen therapy and mechanical ventilation, and the case-fatality ratio (CFR); IRRs for hospitalization rates; and ORs for the risk of severe RSV-ALRI. We subdivided the incidence rate of hospitalization, by age (0 to <12 months and 12 to <24 months), which was not feasible for the other variables, and reported the statistical significance of the difference between the 2 groups. Where age ranges were not the same, we summed the narrower age ranges to a common broader age range. We reported the median age on admission and the LOS descriptively.

Some studies specified underlying CHD as hemodynamically significant, while others did not (Supplementary Table 4). Thus, for outcomes in which both categories of underlying CHD were included (ie, ICU admission, need for mechanical ventilation, and the CFR), we conducted subgroup analysis and reported the statistical significance of the difference between these 2 groups. Subgroup analysis was not feasible for the hospitalization rates and oxygen supplementation outcomes, as these included only 2 studies each, with underlying CHD specified in one and unspecified in the other. For the risk of severe RSV-ALRI, all studies included were for children with unspecified underlying CHD and thus needed no further restratification. Cases of underlying CHD were not reclassified as cyanotic or acyanotic for meta-analysis, owing to limited data. We used a random-effects model to obtain summary estimates and reported the 95% CIs where applicable. We used the Egger test to assess funnel plot asymmetry as evidence for publication bias, where applicable (ie, for ICU admissions, need for mechanical ventilation, and CFR). Statistical significance was set at a P value of <.05.

RESULTS

We included 18 studies in the review, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol (Supplementary Figure 1 and Supplementary Table 5). The overall quality of the studies was of medium grade (average score, 3.6 of 8.0; Supplementary Tables 2 and 3); 5 were of low quality (score, <2.5), 12 were of moderate quality (score, 2.5 to ≤5.0), and 1 was of high quality (score, >5.0

to 8.0). Only for oxygen supplementation (I^2 of 97%; $P < .001$) and mechanical ventilation (I^2 of 94%; $P < .001$) was evidence of significant heterogeneity observed. There was no evidence of publication bias for the tested outcomes: $P = .32$ for ICU admission, $P = .75$ for mechanical ventilation, and $P = .88$ for CFR.

Hospitalization Rates

Two studies reported hospitalization rates per 1000 children [20, 21]. Because one included children aged <24 months [21] and the other included children aged <36 months [20], we divided the results into 2 subgroups by age (0 to <12 months and 12 to <24 months), to combine the 2 studies. Overall, children aged 0–24 months with underlying CHD had a 2.8-fold (95% CI, 1.9–4.1-fold) higher risk of hospitalization than children without CHD (Supplementary Figure 2). Among children aged 0 to <12 months, the mean hospitalization rate was 102.5 events/1000 children for those with underlying CHD and 35.2 events/1000 children for those with no CHD (IRR, 2.5; 95% CI, 1.4–4.5); among those aged 12 to <24 months, rates were 11.5 events/1000 children and 3.0 events/1000 children, respectively (IRR 3.8, 95% CI, 1.5–9.3). Difference in the risk of hospitalization between the 2 age groups was not statistically significant ($P = .46$). Boyce et al reported a hospitalization rate of 4.8 events/1000 children with underlying CHD and 1 event/1000 children without CHD among those aged 24 to <36 months [20]. Two population-based studies reported the proportion of hospitalizations among children with underlying CHD and those without CHD [21, 23], rather than providing incidence rates per 1000 children, with an RR of 3.7 (95% CI, 1.5–9.0) for the group with underlying CHD group, using the group without CHD as a reference. Four studies reported the proportion of hospitalizations for children with underlying CHD but not for those without CHD, Andres et al reported a proportion of 21.1% (15 children) [16] and Feltes et al reported a proportion of 9.7% (63 children) [11] among participants with hemodynamically significant underlying CHD, whereas MacDonald et al reported a proportion of 37.0% (27 children) [8] and Saji et al reported a proportion of 0.9% (83 children, all in the placebo group) [18] among participants with unspecified underlying CHD.

Median Age on Admission and LOS

Two studies reported the median age in months on admission and the LOS, only for children aged <24 months. Median ages were 5.7 months (range, 2.1–19.4 months) for children with underlying CHD versus 4.3 months (range, 1.1–23.6 months) for those without CHD in one study [21] and 7.0 months (range, 0–23.0 months) versus 6.0 months (range, 0–23.0 months) [24], respectively, in the other. The median LOS was 6.5 days (range, 2.0–41.0 days) for children with underlying CHD and 5.0 days (range, 1.0–30.0 days) for those without CHD in the study by Duppenthaler et al [21], with values of 6.0 days (range, 2.0–14.0 days) and 4.0 days (range, 1.0–41.0 days), respectively, in the article by Fjaerli et al [24].

ICU Admissions

Five studies provided data on ICU admissions [8, 21, 22, 23, 26]. Children with underlying CHD had a 3.9-fold (95% CI, 3.4–4.5-fold) higher risk of ICU admission as compared to those without CHD (Supplementary Figure 3). Upon further stratification, children with hemodynamically significant CHD had a 5.0-fold (95% CI, 2.9–8.9-fold) higher risk and those with unspecified CHD had a 3.9-fold (95% CI, 3.3–4.5-fold) higher risk, compared with children without CHD. The difference in risk between the hemodynamically significant CHD group and the unspecified CHD group was not significant ($P = .37$). Two studies provided data on the proportion of hospitalized hemodynamically significant CHD RSV cases that required ICU admission, with values of 40% (6 of 15 children) [16] and 38.1% (24 of 63 children) [11].

Oxygen Supplementation

Two studies reported data on the need for supplemental oxygen therapy. Children with underlying CHD had a 3.4-fold (95% CI, .5–21.1-fold) higher risk of requiring oxygen supplementation, compared with those without CHD (Supplementary Figure 4) [7, 21]. One study reported the median duration of oxygen supplementation, with values of 5 days (range, 1–34 days) for children with underlying CHD and 2 days (range, 0–26 days) for children without CHD [21].

Mechanical Ventilation

Seven publications reported data on the need for mechanical ventilation (Supplementary Figure 5) [7, 8, 13, 21, 22, 17, 27]. Only 1 study reclassified underlying CHD cases as cyanotic or acyanotic, and all 6 recorded cases were acyanotic [13]. Overall, children with underlying CHD had a 4.1-fold (95% CI, 2.1–8.0-fold) higher risk of needing mechanical ventilation as compared to those without CHD. By subgroup, children with hemodynamically significant underlying CHD had a 4.8-fold (95% CI, 4.6–5.1-fold) higher risk and those with unspecified underlying CHD had a 3.4-fold (95% CI, 1.1–11.0-fold) higher risk of needing mechanical ventilation, compared with children without CHD. The difference in risk between the hemodynamically significant CHD group and the unspecified CHD group was not significant ($P = .56$). One study that included only children with unspecified underlying CHD reported that 19.3% of children (16 of 83; all in the placebo group) required mechanical ventilation [18]. Two others provided data only on children with hemodynamically significant underlying CHD, with 5 children (33.0%) [16] and 14 children (22.2%) [11] needing mechanical ventilation. Only one study reported on the duration of mechanical ventilation, with a mean difference of 11.3 days between children with unspecified underlying CHD and those without CHD [13].

Risk of Severe RSV-ALRI

Three studies reported unspecified underlying CHD as a risk factor for severe RSV-ALRI, using multivariable analysis (other variables included were clinical signs of severe disease, such as apnea, abnormal blood gas levels, LOS >5 days, need for supplemental oxygen therapy, and need for mechanical ventilation). Rodriguez et al reported an RR of 2.0 (95% CI, 1.2–3.5) [28], Kaneko et al reported an OR of 99.2 (95% CI, 8.5-1160.1) [7], and Zhang et al reported an OR of 2.3 (95% CI, 1.7–3.1) [1]. By assuming that the RR of 2.0 reported by Rodriguez et al [28] is equivalent to the OR (because severe RSV-ALRI with underlying CHD is rare), we conducted a meta-analysis of these ORs and obtained an OR of 2.2 (95% CI, 1.6–2.8).

Risk of RSV-ALRI–Associated Death

Eight studies reported mortality data (Table 1). We observed a higher overall CFR among those with underlying CHD as compared to those without CHD [8, 21, 22, 17, 27]. Two studies reported a lower CFR among children with unspecified underlying CHD as compared to those without CHD [12, 28], while 1 study reported no death in either group [7]. Children with underlying CHD had a 16.5-fold (95% CI, 13.7–19.8-fold) higher risk of RSV-ALRI–associated death overall, compared with children without CHD. By subgroup, those with hemodynamically significant underlying CHD had a 17.9-fold (95% CI, 14.9–21.6-fold) higher risk, whereas the group with unspecified underlying CHD had a 9.6-fold (95% CI, 8.9–10.4-fold) higher risk, compared with the group without CHD. The difference in risk between the hemodynamically significant CHD group and the unspecified CHD group was not significant ($P = .22$).

DISCUSSION

Our review demonstrated that the severity of RSV-ALRI was higher among children with underlying CHD as compared to those without CHD, especially with regard to the need for hospitalization, intensive care management, respiratory support, and that underlying CHD was associated with an increased CFR, compared with no CHD.

The higher risk for hospitalization in the group with underlying CHD could be due to higher severity of the disease in children with underlying CHD or a result of physician behavior when deciding whether to admit those with perceived risk factors. We also found that the age-related risk of hospitalization for RSV-ALRI among children with underlying CHD was more widely distributed as compared to that among children without CHD, similar to findings from an earlier publication, which reported a mean age (±SD) of 6.3 ± 6.0 months among admitted patients with underlying CHD, compared with 3.5 ± 3.3 months in the healthy group [29].

Risks for all the measured outcomes were higher in the group with underlying CHD, compared with the non-CHD group. High rates of hospitalization, ICU admission, and death among children with RSV-LRTI and underlying CHD were also reported by other studies, but they did not fulfill the criteria for inclusion in our review [30, 31]. Sensitivity analysis revealed a higher effect among cases of hemodynamically significant underlying CHD, compared with cases of unspecified underlying CHD. Although the small sample size in some of the studies could have affected the statistical significance of findings, these data suggest that the severity of RSV-ALRI displayed a trend toward a positive association with the severity of underlying CHD. The higher severity of RSV-ALRI in the group with underlying CHD could have severe long-term implications on the children's health and the cost of their care. In addition, RSV infection may delay cardiac surgery, and during the convalescence phase there is an increased risk of a more severe disease outcome and possible long-term complications [30, 32, 33]. Because underlying CHD has been associated with increased RSV-ALRI severity, such a group will be a useful target for preventive measures.

Despite the availability of palivizumab for immunoprophylaxis, there are significant differences in the guidelines for its use, such as those from the French Society of Cardiology [34] and the American Academy of Pediatrics (AAP) [12, 13]. These differences could be a challenge in formulating a standard universal protocol for palivizumab use. The updated AAP recommendation for the use of palivizumab in children with hemodynamically significant CHD still includes only children aged <1 year [35] and is probably based on the finding by Boyce et al that the rate of RSV-associated hospitalization among children with CHD aged >1 year was not higher than that among low-risk children [20]. However, other outcome measurements that could define the severity of RSV-ALRI among hospitalized children, such as the need for ICU admission, supplemental oxygen therapy, mechanical ventilation, or the risk of RSV-ALRI–associated death, were not assessed in this study. Thus, hospitalized children with hemodynamically significant underlying CHD may have a more severe disease progression as compared to those without CHD, as shown in our review, in which the rate of RSV-ALRI–associated hospitalization was higher among children in the second year of life as compared to those in the first year. Furthermore, the international multicenter randomized controlled trial that demonstrated benefits of palivizumab prophylaxis in children with hemodynamically significant underlying CHD, including a decrease in the RSV-associated hospitalization rate and the duration of supplemental oxygen supplementation therapy in this group as compared to the placebo group (with a greater decrease among children with acyanotic hemodynamically significant CHD than among with cyanotic hemodynamically significant underlying CHD), included children up to 24 months of age [11, 36]. Considering that the study lasted up to 4 years, with benefits recorded throughout this period, the beneficial effect of palivizumab prophylaxis in children with hemodynamically

significant underlying CHD may go even beyond 2 years of age. Other professional societies include children aged <2 years under certain conditions in their recommendations, such as those in France and Germany and, more recently, an international committee of experts, whereas the British Congenital Cardiac Association and Joint Committee on Vaccination and Immunization guidelines also include children older than 1 year with complex heart disease in their recommendation for immunoprophylaxis based on clinical judgment [37]. With improvement in cardiac surgical care, those with underlying CHD who are older than 1 year of age may increasingly represent the more severe spectrum of underlying CHD for whom immunoprophylaxis may be of greatest benefit.

This report has several strengths and limitations. We have included studies from North America, South America, Europe, and Asia but none from Africa. This limitation and the heterogeneity of the data make generalization of the results difficult. The limited data on certain outcomes, such as duration of supplemental oxygen therapy, made it difficult to synthesize the data for such outcomes and were therefore only reported descriptively. There was no standard case definition of RSV-ALRI infection, underlying CHD, or hemodynamically significant underlying CHD. Other underlying conditions (eg, prematurity) that may have biased outcome measurements were not highlighted by some of the studies. Most of the included studies were retrospective studies, from which evidence is less strong. These factors and the lack of proper matching affected the quality of the studies (medium grade overall).

There were scarce data available for children with underlying CHD aged >24 months, thus limiting the conclusions that may be drawn for those who are 2–4 years of age with underlying CHD. Additional data are required on the effects of RSV-ALRI in this population, both before and after cardiac surgery, before the effects of RSV infection on corrective cardiac surgery can be assessed in a meta-analysis.

Only 6 of 18 included studies specified the underlying CHD cases as hemodynamically significant, and only 1 study reclassified the cases of underlying CHD (unspecified) into cyanotic and acyanotic, albeit just for 1 outcome (need for mechanical ventilation) [13]. Thus, subgroup analysis based on cyanotic and acyanotic criteria was not feasible. Although all included cases that required mechanical ventilation were acyanotic and because the benefits of palivizumab prophylaxis in children with hemodynamically significant underlying CHD are shown to be higher in this group (as mentioned earlier), we did not have enough evidence to prove this.

In summary, children with RSV with underlying CHD, especially hemodynamically significant underlying CHD, have more severe RSV-ALRIs than those without CHD. Our analysis identifies an unmet requirement for preventive therapies and treatments to reduce the high risk of morbidity and mortality associated with RSV infection in those with underlying CHD. The introduction and acceptance of a standardized disease classification for underlying CHD and hemodynamically significant underlying CHD would enable proper case definition, thus enhancing the feasibility and comparability of investigational studies of preventive therapies and treatments. Furthermore, recommendations and application of preventive and treatment guidelines for underlying CHD should include older children, because the risk of higher morbidity and mortality is not limited to children aged <1 year.

STUDY GROUP MEMBERS

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Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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